

II. Rejection of claims 1-6 and 8-17 under 35 U.S.C. § 103(a)

Claims 1-6 and 8-17 were rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,213,811 to Frisbee et al. ("Frisbee") in view of WO 93/21921 to Haikala et al. ("Haikala"), or vice versa. In support of the rejection, the Examiner stated that Frisbee teaches a "sustained release drug composition comprising two different release profile compositions." The Examiner mentioned that one component is a sustained release composition and the second is a rapid release composition. The Examiner characterized the sustained release component as comprising a bead having a coating of drug, hydroxypropyl methylcellulose and a plasticizer, then further coated with a mixture of ethyl cellulose, hydroxypropyl cellulose, polyvinyl acetate phthalate and a plasticizer. The Examiner characterized the rapid release component as having the same coatings as the sustained release component, but also having an additional coating of the drug layer on the outside of the bead or as an end layer. Frisbee notes that one example drug in its compositions is milrinone.

The Examiner acknowledged that Frisbee does not expressly teach levosimendan as an active agent or concentration ranges of certain specific components. The Examiner identified Haikala, however, as teaching levosimendan as a known anti-ischemic drug. The Examiner concluded that it would have been obvious to combine the teaching of Frisbee with the teachings of Haikala to make the claimed invention, as levosimendan and milrinone are both PDE III inhibitors. Applicants respectfully traverse this rejection.

The compositions of the Frisbee disclosure are stated to be "sustained-release" compositions. Col. 1 at lines 7-8. The first composition, cited by the Examiner at col. 2, lines 19-21, is disclosed as providing sustained release of the drug as the composition passes through the gastrointestinal tract. The second composition, cited by the Examiner at col. 2, lines 27-30, provides an initial rapid release of the drug, but then, similar to the first composition, provides sustained release of the drug as the

composition passes through the gastrointestinal tract. Thus, in both cases, the composition provides sustained release of the drug through the gastrointestinal tract.

One skilled in the art would not have been motivated to combine the teachings of Frisbee and Haikala to make the claimed inventions. Frisbee states that its compositions are intended for drugs that are highly soluble in gastric fluid and much less soluble in intestinal fluid. Frisbee at col. 1, lines 10-11. It more specifically describes those drugs as ones having a solubility of at least 5% by weight in gastric fluid and less than 1% by weight in intestinal fluid. Frisbee at col. 2, line 67 to col. 3, line 1. Levosimendan is weakly acidic, having a pKa of about 6.3, and is therefore not a basic drug. As a result, the solubility of levosimendan is better in the intestine (an environment of relatively high pH) than in the stomach (an environment of relatively lower pH). This solubility profile of levosimendan is opposite that of drugs intended for the Frisbee compositions. Thus, one skilled in the art would have been detracted from making the proposed combination of references, rather than being motivated to do so.

Claim 1 furthermore recites that the drug release controlling component in the claimed composition provides for the release of levosimendan in a way that produces a steady-state plasma level for the levosimendan metabolite (II) of less than 20 ng/ml. As explained in the specification at page 2, lines 20-26, the metabolite (II) forms as a first-pass metabolite in the large intestine. The metabolite (II) can accumulate to cause undesirable effects such as severe headache, palpitation and increased heart rate. Specification at page 3, lines 26-28.

Neither of Frisbee and Haikala, alone or in combination, teach or suggest this plasma level element of the claim. None of the documents speculate on the formation of metabolites of the drugs they disclose. Neither appear to appreciate what effects such metabolites may have or motivate one skilled in the art to reduce the levels of such metabolites. Instead, compositions such as Frisbee's, which are designed to provide sustained release of drug "through the gastrointestinal tract," would seem to favor significant formation of metabolite (II), as levosimendan is particularly susceptible

to metabolization in the large intestine. For these additional reasons, the cited documents do not create a *prima facie* case of obviousness of claim 1.

The composition of claim 4 is a controlled release composition wherein the total *in vitro* dissolution time determined according to the USP XXII basket assembly method in phosphate buffer pH 5.8 ranges from about 1 to about 4 hours for at least 90 percent of the content of levosimendan. As explained in the specification at page 13, lines 14-18, this formulation yields significantly lower plasma levels of metabolite (II) than reference formulations that have slower *in vitro* dissolution rates.

Neither of Frisbee and Haikala, alone or in combination, teach or suggest the *in vitro* dissolution element of claim 4. None of the documents even report *in vitro* data for any of their disclosed compounds. The disclosure of the Frisbee compositions as providing sustained release of drug "through the gastrointestinal tract" indicates an absence of concern or appreciation for the formation of undesirable metabolites. Frisbee certainly does not suggest that or any other significant factor as motivation for choosing compositions having *in vitro* profiles as claimed compared to others. For these additional reasons, the cited documents do not create to a *prima facie* case of obviousness of claim 4.

III. Rejection of claim 7 under 35 U.S.C. § 103(a)

Claim 7 was rejected under 35 U.S.C. § 103(a) as unpatentable over Frisbee in view of Haikala further in view of EP 0 091 767 to Yarwood et al. ("Yarwood"). Claim 7 recites that the rapid release portion of claim 5 comprises levosimendan and microcrystalline cellulose. The Examiner acknowledged that Frisbee and Haikala do not teach the use of microcrystalline cellulose as an excipient, but that it would have been obvious to use it as disclosed in Yarwood as a pharmaceutical component.

As explained above, one skilled in the art would not have been motivated to combine the two Frisbee and Haikala disclosures as proposed by the Examiner. One skilled in the art therefore would not have been motivated to combine those two teachings all together with the disclosure of Yarwood. Furthermore, the Examiner relied


on Yarwood simply for a teaching of microcrystalline cellulose. This teaching does not render the claimed invention obvious or supply the motivation that is lacking to combine the two Frisbee and Haikala disclosures in the first place. Claim 7 should thus be patentable over the cited documents.

If there is any fee due in connection with the filing of this Response, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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